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Clinical Investigation

Nomograms for Prediction of Outcome With or Without Adjuvant Radiation Therapy for Patients With Endometrial Cancer: A Pooled Analysis of PORTEC-1 and PORTEC-2 Trials



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Summary

To facilitate treatment decision support for individual patients with early stage endometrial cancer, nomograms were developed from the PORTEC-1 and -2 databases (N = 1240 patients) to predict the individual patient's risk of locoregional relapse, distant relapse, overall survival, and disease-free survival. These

Background: Postoperative radiation therapy for stage I endometrial cancer improves locoregional control but is without survival benefit. To facilitate treatment decision support for individual patients, accurate statistical models to predict locoregional relapse (LRR), distant relapse (DR), overall survival (OS), and disease-free survival (DFS) are required.

Methods and Materials: Clinical trial data from the randomized Post Operative Radiation Therapy for Endometrial Cancer (PORTEC-1; N = 714 patients) and PORTEC-2 (N = 427 patients) trials and registered group (grade 3 and deep invasion, n = 99) were pooled for analysis (N = 1240). For most patients (86%) pathology review data were available; otherwise original pathology data were used. Trial variables which were clinically relevant and eligible according to data constraints were age, stage, given treatment (pelvic external beam radiation therapy (EBRT), vaginal brachytherapy (VBT), or no adjuvant treatment, FIGO histological grade, depth of invasion, and lymph-vascular invasion (LVSI). Multivariate analyses were based on

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nomograms are indispensable for patient counseling and shared decision making, especially as they include the effect of external beam radiation therapy or vaginal brachytherapy on the risks of locoregional relapse and disease-free survival.

Cox proportional hazards regression model. Predictors were selected based on a backward elimination scheme. Model results were expressed by the c-index (0.5-1.0; random to perfect prediction). Two validation sets (n=244 and 291 patients) were used.

Results: Accuracy of the developed models was good, with training accuracies between 0.71 and 0.78. The nomograms validated well for DR (0.73), DFS (0.69), and OS (0.70), but validation was only fair for LRR (0.59). Ranking of variables as to their predictive power showed that age, tumor grade, and LVSI were highly predictive for all outcomes, and given treatment for LRR and DFS. The nomograms were able to significantly distinguish low- from high-probability patients for these outcomes.

Conclusions: The nomograms are internally validated and able to accurately predict long-term outcome for endometrial cancer patients with observation, pelvic EBRT, or VBT after surgery. These models facilitate decision support in daily clinical practice and can be used for patient counseling and shared decision making, selecting patients who benefit most from adjuvant treatment, and generating new hypotheses.

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Introduction

Endometrial cancer (EC) is the most common gynecological cancer in developed countries. Surgery is the cornerstone of treatment. Postoperative pelvic external beam radiation therapy (EBRT) for early stage EC has been shown in multiple randomized trials to significantly increase locoregional control but has no impact on overall survival (OS) (1, 2). The indication for adjuvant RT is tailored to the risk of recurrence. This spares most EC patients with a favorable prognosis the negative effects of pelvic EBRT, and significantly reduces the risk of disease recurrence, with its associated anxiety and stress, and the toxicities of salvage treatment in the minority of patients who are at higher risk (3). Using pelvic EBRT for patients with low-risk disease may even negatively affect their eventual outcome (2, 4).

For EC patients with high-intermediate risk factors, vaginal brachytherapy (VBT) alone has been shown to result in excellent vaginal cancer control, without the short- and long-term toxicities of EBRT (5, 6). To refine the indication for adjuvant therapy among patients with risk factors and to identify the occasional patient with higher risk among those with a low-risk profile, studies of molecular genetic risk factors are increasingly being done, and some have shown promising results (7, 8).

When patients are asked about their treatment preferences, in most cases they favor adjuvant treatment to ensure they have used all possible treatments to reduce the risk of cancer recurrence. In addition, they do wish to be involved in clinical decision making and be informed about the risk and benefits of alternative treatment options, and make an informed, joint decision together with their physician (9, 10).

Recently, treatment decision support nomograms have been developed by several groups to facilitate patient

information and counseling based on their individual situation and individual risks of local, regional, and distant recurrence. Such systems have been based on large databases of historical patients and have incorporated various patient and tumor characteristics and outcomes (11-13). The Australian nomogram, which is also available as a mobile phone application, has been based on results of 2097 patients and is focused on assessing the individual patient's risk of isolated locoregional and distant recurrence (12). The Memorial Sloan-Kettering Cancer Center nomogram informs on the risk of 3-year OS, without differentiating between local and distant relapse (DR) (11). The most recent nomogram, developed by AlHilli et al (13), is focused on assessing the individual patient's risk of (microscopic) pelvic lymph node metastases, to be used for patient counseling regarding the indication for second surgery; they used clinical data from 883 patients treated over a 10-year time period.

None of the previous studies has been able to include adjuvant treatment modalities in the risk prediction models, as adjuvant treatment had not been used consistently over the long study periods. This would require a patient cohort in which adjuvant treatment was used consistently and preferably randomly allocated. For most patients with early stage disease, the inclusion of outcomes with or without adjuvant RT, specifically pelvic EBRT and VBT, would be highly desirable to facilitate individual patient counseling on the risks and benefits of using adjuvant treatment in their particular situation.

We combined the databases from the randomized Post Operative Radiation Therapy for Endometrial Cancer (PORTEC)-1 and PORTEC-2 trials and used this pooled patient data set, in which adjuvant treatment had been randomly allocated to develop such treatment decision support nomograms, including outcomes with and without adjuvant treatment.

Methods and Materials

Patient and tumor characteristics

Clinical trial data from the PORTEC-1 (N=714 patients) and PORTEC-2 (N=427 patients) trials and the PORTEC registration group with grade 3 and deep invasion (N=99 patients) were pooled for this analysis, providing a total number of 1240 patients. In the PORTEC-1 trial, patients with stage I EC with low-intermediate and high-intermediate risk features were randomly allocated to adjuvant EBRT and observation after surgery (14, 15). In the PORTEC-2 trial, patients with stage I EC (and International Federation of Gynecology and Obstetrics [FIGO] 1988 stage IIA, which are classified as stage I in the 2009 FIGO staging) with high-intermediate risk factors were randomly allocated to pelvic EBRT or VBT (5). During the inclusion period of the PORTEC-1 trial, stage I patients with high-risk factors (grade 3 with deep myometrial invasion) were not randomized but were registered, and all received adjuvant pelvic EBRT (16). Finally, 2 validation sets were used. The first was obtained from the Maastricht radiation oncology retrospective database, including all patients who fitted the inclusion criteria for PORTEC-1 and PORTEC-2 trials and the high-risk registry group (but who were not included in those trials) and who had been treated between 1978 and 2010 (n=244 patients). The second validation set was obtained from the Medisch Spectrum Twente Enschede endometrial carcinoma database, which included all patients who fitted the same criteria and had been treated for FIGO 1988 stages I to IIA between August 1988 and March 2014, with exclusion of those patients who had participated in one of the PORTEC trials (n=291 patients).

Patient and tumor characteristics and outcome data were obtained from the trial databases (Tables 1 and 2) (5, 15). Data from the pathology review from both trials were used if available (80% for PORTEC-1 and 90% for PORTEC-2; overall 86%); otherwise, original pathology data were used. Age was calculated at the time of randomization. Time-to-event analyses were done from the date of surgery, as this date was available for all patients, including the registered and validation groups. Patients lost to follow-up (n=42) were considered censored at the day of last follow-up. Median follow-up for patients alive was 160 months for PORTEC-1 and 89 months for PORTEC-2 and 213 and 90 months for the Maastricht and Enschede validation sets, respectively.

Initially, the following variables were selected as clinically relevant for follow-up outcome: FIGO 1988 (sub) stage, age, FIGO grade, depth of myometrial invasion, width of the uninvolved myometrium, distance between the point of deepest tumor invasion to the serosal surface, lymph-vascular space invasion and/or angioinvasion, involvement of the cornuae (uterine cornua or horns), and treatment given. Variables that were not used because the percentage of missing values was too high or variation

Table 1 Trial and treatment information

Parameter	No. of patients (%)
Treatment group	
PORTEC-I	714 (57.6)
PORTEC-II	427 (34.4)
Registered group*	99 (8.0)
Given treatment	
EBRT	648 (52.3)
VBT	214 (17.3)
Observation	378 (30.4)
Randomized treatment	
EBRT	667 (53.8)
VBT	213 (17.2)
Observation	360 (29.0)
Validation group Maastricht	
EBRT	150 (61.5)
VBT	94 (38.5)
Observation	0 (0.0)
Validation group Enschede	
EBRT	203 (69.8)
VBT	88 (30.2)
Observation	0 (0.0)

Abbreviations: EBRT = pelvic external beam radiation therapy; VBT = vaginal brachytherapy.

* Registered patients with grade 3 and outer myometrial invasion were all given EBRT.

power of values was too low included FIGO 1988 (sub) stage (deterministic with myometrial invasion and grade), width of the uninvolved myometrium, and distance from the serosa (too many missing values). Peritoneal cytology was not taken into account because of the rarity of malignant findings.

Clinical, pathologic, and treatment variables were tested for significance. The variables that were used in the final analysis were age (as continuous variable), treatment given (pelvic EBRT, VBT, or no adjuvant treatment), FIGO histological grade, depth of myometrial invasion, involvement of the cornuae uteri (where the myometrium is thinnest), and lymph-vascular space invasion (LVSI) and/or angioinvasion. Outcome data were defined as vaginal relapse (VR), pelvic relapse (PR), combined locoregional relapse (LRR [vaginal and/or pelvic]), DR, OS, and disease-free survival (DFS).

OS was taken from date of randomization or surgery (for nontrial patients) with failure defined as death regardless of the cause and censored at the date of last contact for patients still alive; for DFS, with failure taken as death or relapse, whichever occurred first, and censored at the date of last contact for patients still alive and disease free.

Statistical methods

Any missing values were imputed by the expectation-maximization algorithm. Data were normalized (mean, 0; standard deviation, 1) before any analysis was performed.

Table 2 Patient characteristics of the initial and final pooled trial cohort and the validation sets

Characteristic	Initial pooled trial cohort*	Final trial cohort*	Validation Maastricht	Validation Enschede
	N (%)	n (%)	n (%)	n (%)
Total	1240	1240	244	291
Age (y)				
Median	68.0	68.0	65.8	68.0
Range	35.2-92.2	35.2-92.2	19.5-86.8	44.0-92.0
FIGO histological grade				
1	344 (27.7)	730 (58.9)	93 (38.1)	96 (33.0)
2	689 (55.6)	256 (20.6)	124 (50.8)	98 (33.7)
3	207 (16.7)	254 (20.5)	20 (8.2)	91 (31.3)
Unknown	0 (0)	0 (0)	7 (2.9)	6 (2.1)
Myometrial invasion				
<50%	352 (28.4)	368 (29.7)	110 (45.1)	77 (26.5)
>50%	888 (71.6)	872 (70.3)	131 (53.7)	214 (73.5)
Unknown	0 (0)	0 (0)	3 (1.2)	0 (0)
Invasion of cornuae				
No	865 (69.8)	886 (71.5)	176 (72.1)	291 (100)
Yes	333 (26.9)	324 (26.1)	41 (16.8)	0 (0)
Unknown	42 (3.4)	30 (2.4)	27 (11.1)	0 (0)
Vascular invasion				
No	1046 (84.4)	1106 (89.2)	192 (78.7)	246 (84.5)
Yes	111 (9.0)	117 (9.4)	52 (21.3)	45 (15.5)
Unknown	83 (6.7)	17 (1.4)	0 (0)	0 (0)
Radiation therapy				
None	378 (30.5)	378 (30.5)	0 (0)	0 (0)
EBRT	648 (52.3)	648 (52.3)	150 (61.5)	203 (69.8)
VBT	214 (17.3)	214 (17.3)	94 (38.5)	88 (30.2)

Abbreviations: EBRT = pelvic external beam radiation therapy; FIGO = International Federation of Gynecology and Obstetrics; VBT = vaginal brachytherapy.

* Initial refers to the pooled trial cohort with original pathology data; the final trial cohort, which was used for analysis, included revised pathology data (available for 86% of the patients) and substituted original pathology data for the 14% for whom no pathology review was available.

Multivariate analyses were based on the Cox proportional hazard model, and model performances using the censored outcome data were assessed by the c-index. This index has properties similar to area under the receiver operating characteristic curve (0.5, random prediction; 1, perfect prediction). The variable “given treatment,” was replaced by 2 dummy variables for EBRT and VBT because the specific order of the values does not have a meaning (ie, the variable is not ordinal). Age was treated as a continuous variable and FIGO grade as an ordinal variable, and the other invasion-related variables were converted to binary variables (no, yes), which meant they were nominal in the analysis.

Identifying the predictors, that is, the variables that have a significant association with outcome, was done in a multivariate setting, using a backward elimination process. In this method, one starts with all variables in the multivariate model and tests for significance. In each subsequent iteration, the least significant variable was excluded, and the new combination of variables was tested again. This process was repeated until all variables were predictive ($\alpha = .05$). This final predictor set was used to develop the nomograms, which are visual representations of the trained Cox models. Performance of the nomograms was

calculated by using bootstrapping in which the evaluated data set was tested 1000 times, and each time, data were randomly resampled (patients could occur in the data set more than once), and c-index was calculated. The final step was to compute the average bootstrapped performance and its 95% confidence interval. Calibration, that is, predicted event rates versus observed event rates, was assessed by plotting these quantities in subgroups with equal numbers of patients (training: 9; subgroups, merged validation: 6 subgroups). The Hosmer-Lemeshow statistic was used to test significance of the calibration (in this test, significant P values relate to poor calibration).

Results

Patient outcomes

Among the total of 1240 patients in our analysis, 648 (52.3%) had received adjuvant pelvic EBRT, 214 (17.3%) had received VBT, and 378 (30.4%) had been observed after surgery. Further treatment information and trial origins are reported in [Table 1](#). Patient characteristics of the pooled trial cohorts and validation sets are shown in

Table 2. Rates of vaginal and pelvic recurrence, distant metastases, and OS and DFS are shown in [Table 3](#).

Nomogram development

For the development of the nomograms, the complete pooled dataset with the PORTEC patients and the PORTEC registration group with grade 3 and deep myometrial invasion was used (N=1240 patients). These data were updated for the pathology review ([Table 2](#)). The backwards elimination method for predictor selection resulted in multiple predictors for the 4 assessed outcomes: LRR, DR, DFS, and OS ([Table 4](#)). The predictors age, FIGO grade, and LVSI were consistently selected for all outcomes. Age (in years) had the highest hazard ratios (HR) for DFS (HR = 1.77) and OS (HR = 1.94) compared to the other predictors, and FIGO grade had the highest HR for LRR (HR = 1.64) and DR (HR = 1.96). Myometrial invasion was selected for LRR, DR, and DFS but was not associated with OS. Invasion of cornuae was not selected and was therefore left out of the nomogram. LVSI was selected for all outcomes (HR = 1.1-1.2). All demographic and clinical predictors had HR of >1, meaning that higher age, higher grade, and myometrial invasion or increase in invasion depth are associated with a worse prognosis.

Treatment variables were associated with LRR and DFS (HR < 1: both treatments improved these outcomes) but not with DR and OS. This implies that pelvic EBRT and VBT reduce LRR but do not result in improved OS, which is highly driven by age and distant recurrence: 5-year OS was

88.3% for DR-free patients versus 18.2% for patients with DR. For LRR and DFS, the RT variables were selected, which suggests that for those outcomes, the observational patient group is an important reference group when reporting the association of RT modalities with outcome. The resulting nomograms ([Fig. 1](#)) are able to estimate outcome probabilities for each specific outcome by assigning a score ([Fig. 1](#), upper scale “Score”) to each predictor value. The sum of these scores corresponds to an event probability.

Nomogram validation

Performances of the nomograms are reported in [Table 4](#) for both the training set (N=1240) and the 2 validation sets (n=244 and 291). Highest training c-indices were reported for LRR (0.78; 95% confidence interval [CI]: 0.73-0.83) and DR (0.76; 95% CI: 0.71-0.81). The performance for DR was reproduced in the validation datasets, with c-indices of 0.64 and 0.76, and 0.73 for the merged set. However, lower c-indices of 0.58 (0.44-0.71) and 0.62 (0.49-0.75) were found for LRR. The survival-related nomograms validated with significant consistency; for DFS, the c-index was 0.71 (95% CI: 0.67-0.74) for training and 0.69 (95% CI: 0.63-0.75) for validation. For OS, the c-index was 0.71 (95% CI: 0.67-0.75) for training, and this validated very well with c-index of 0.70 (95% CI: 0.64-0.76).

[Figure 2](#) shows that the nomograms have a good calibration when tested in both the training and the validation

Table 3 Median follow-up and outcome rates at 5 and 10 years for training and validation datasets

	No. of events	Median follow-up (mo) (95% CI)	Outcome % at 5 y (95% CI)	Outcome % at 10 y (95% CI)
Training (N=1240 patients)				
VR	59	72.4 (66.5-79.4)	4.43 (3.16-5.68)	5.63 (4.05-7.19)
PR	34	74.9 (69.8-82.4)	2.38 (1.42-3.33)	2.95 (1.8-4.09)
LRR	92	74.8 (69.1-82.4)	6.69 (5.13-8.22)	8.44 (6.52-10.3)
DR	114	81.2 (73.8-92.4)	7.17 (5.58-8.73)	8.55 (6.71-10.4)
DFS	428	120 (113-126)	79.8 (77.3-82.3)	67 (63.8-70.3)
OS	393	139 (135-143)	83.7 (81.4-86)	70.9 (67.8-74)
Maastricht (n=244 patients)				
VR	18	59.9 (55-62.4)	7.81 (3.98-11.5)	10.8 (5.15-16.2)
PR	4	57.7 (52.4-61.2)	1.84 (0.035-3.61)	1.84 (0.035-3.61)
LRR	21	59.9 (55-62.3)	9.16 (5.06-13.1)	12.2 (6.33-17.7)
DR	17	59.9 (55.4-62.4)	7.15 (3.39-10.8)	11.2 (4.39-17.4)
DFS	121	102 (82.1-121)	77.9 (72.6-83.5)	60.3 (53.1-68.5)
OS	113	213 (173-247)	82.2 (77.3-87.3)	70 (63.9-76.6)
Enschede (n=291 patients)				
VR	8	66.2 (55.6-77.4)	2.95 (0.91-4.95)	2.95 (0.91-4.95)
PR	15	68.2 (56-78.4)	5.58 (2.65-8.42)	6.41 (3.07-9.64)
LRR	19	69.1 (56.9-80)	6.94 (3.75-10)	7.76 (4.2-11.2)
DR	40	73 (66.4-87)	13.2 (8.94-17.3)	16 (11-20.7)
DFS	90	92.3 (77.9-116)	75.9 (70.7-81.5)	63.9 (57.4-71.2)
OS	81	90.4 (77.9-116)	79.1 (74-84.5)	65.7 (59-73)

Abbreviations: DFS = disease-free survival; DR = distant relapse; LRR = locoregional relapse; OS = overall survival; PR = pelvic relapse; VR = vaginal relapse.

Table 4 HR and corresponding *P* values based on multivariate Cox models for selected prognostic factors with respect to the different endpoints*

Factor	LRR		DR		DFS		OS	
	HR	<i>P</i>	HR	<i>P</i>	HR	<i>P</i>	HR	<i>P</i>
Age	1.35	.006	1.35	.001	1.77	<.001	1.94	<.001
FIGO grade	1.64	<.001	1.96	<.001	1.25	<.001	1.29	<.001
Myometrial invasion	1.50	.001	1.26	.033	1.11	.045	-	-
Invasion of cornuae	-	-	-	-	-	-	-	-
Vascular invasion	1.21	.029	1.21	.007	1.13	.007	1.12	.016
EBRT	0.45	<.001	-	-	0.90	.040	-	-
VBT	0.64	<.001	-	-	0.82	.009	-	-
Training c-index (95% CI)	0.78 (0.73-0.83)		0.76 (0.71-0.81)		0.71 (0.67-0.74)		0.71 (0.67-0.75)	
Validation Maastricht c-index (95% CI)	0.58 (0.44-0.71)		0.64 (0.49-0.78)		0.69 (0.61-0.77)		0.71 (0.62-0.78)	
Validation Enschede c-index (95% CI)	0.62 (0.49-0.75)		0.76 (0.68-0.84)		0.70 (0.62-0.78)		0.70 (0.63-0.77)	
Validation merged c-index (95% CI)	0.59 (0.50-0.68)		0.73 (0.65-0.80)		0.69 (0.63-0.75)		0.70 (0.64-0.76)	

Abbreviations: DFS = disease-free survival; DR = distant relapse; EBRT = pelvic external beam radiation therapy; FIGO = International Federation of Gynecology and Obstetrics; HR = hazard ratio; LRR = locoregional relapse; OS = overall survival; VBT = vaginal brachytherapy.

* For every model the c-index with 95% confidence interval is computed for both the training dataset and the validation datasets and also for the merged validation set.

datasets. Only predictions for LRR were significantly underestimated for the lower risk patients ($P < .0001$). Application of the DFS and OS nomograms to the training and validation datasets, respectively, are shown in [supplementary Figure E3](#) (available online at www.redjournal.com). The median risk probability was used as a threshold to distinguish between high- and low-risk patients. For both outcomes and both datasets, the Kaplan-Meier curves were significantly distinct. This confirms the fact that the nomograms validate well and that they have the potency to distinguish among risk groups based on a multivariate set of predictors.

Use of the nomograms in clinical practice

Examples of the potential use of the nomograms during patient counseling have been described in [supplementary Table E5](#) (available online at www.redjournal.com). This shows that the nomograms are especially valid for use when counseling patients with intermediate- and high-intermediate-risk stage I endometrial carcinoma (the risk groups on which the nomograms have been built). For patients with all high-risk factors (advanced age, grade 3, LVSI, deep invasion), the model may slightly overestimate events.

Discussion

This pooled analysis of outcome data of 1240 EC patients treated in the randomized PORTEC-1 and PORTEC-2 trials was done to construct nomograms which could be used to predict long-term outcome after surgery with or without pelvic EBRT or VBT. Because of the random treatment allocation, the complete follow-up information, and the large number of patients, the pooled trial databases

provided unique data with which to reliably analyze such outcomes. The nomograms are able to accurately predict long-term outcome in terms of LRR, DR, and survival with or without adjuvant treatment and have been externally validated for survival.

All of the previously developed nomograms were able to predict the likelihood of relapse and survival based on prognostic factors. For example, the Australian nomogram application is used in clinical practice for discussing individual patients' risks of disease recurrence based on clinical-pathological prognostic factors (12). Likewise, the Mayo Clinic nomogram is used to counsel a patient on the risks and benefits of second staging surgery based on the patient's individual risk of having microscopic pelvic lymph node metastases (13).

The nomograms provided in this study are unique in that they are the first set of nomograms that include information for outcomes with or without adjuvant EBRT or VBT. With this inclusion of adjuvant treatment, these nomograms are the ideal basis for individual patient information and counseling. Both can be used after endometrial tissue sampling and/or after definitive surgery for shared decision making in daily clinical practice.

Decisions about the minimal benefit required to justify adjuvant therapy as made by local or national guideline committees do not allow for such individual preferences and informed decisions. In view of the absence of a survival benefit, RT for early stage EC (with or without risk factors) was uniformly abandoned in Denmark (17). Recent results of a Danish cancer registry study show that without adjuvant pelvic EBRT or brachytherapy, 22% of EC patients with intermediate risk factors will experience a relapse, and 14% of the 22% will have a locoregional recurrence (18). PORTEC-2 data suggest that the majority of these recurrences (12% of these 14%) could have been prevented with VBT (5). Patients should be aware of these facts and

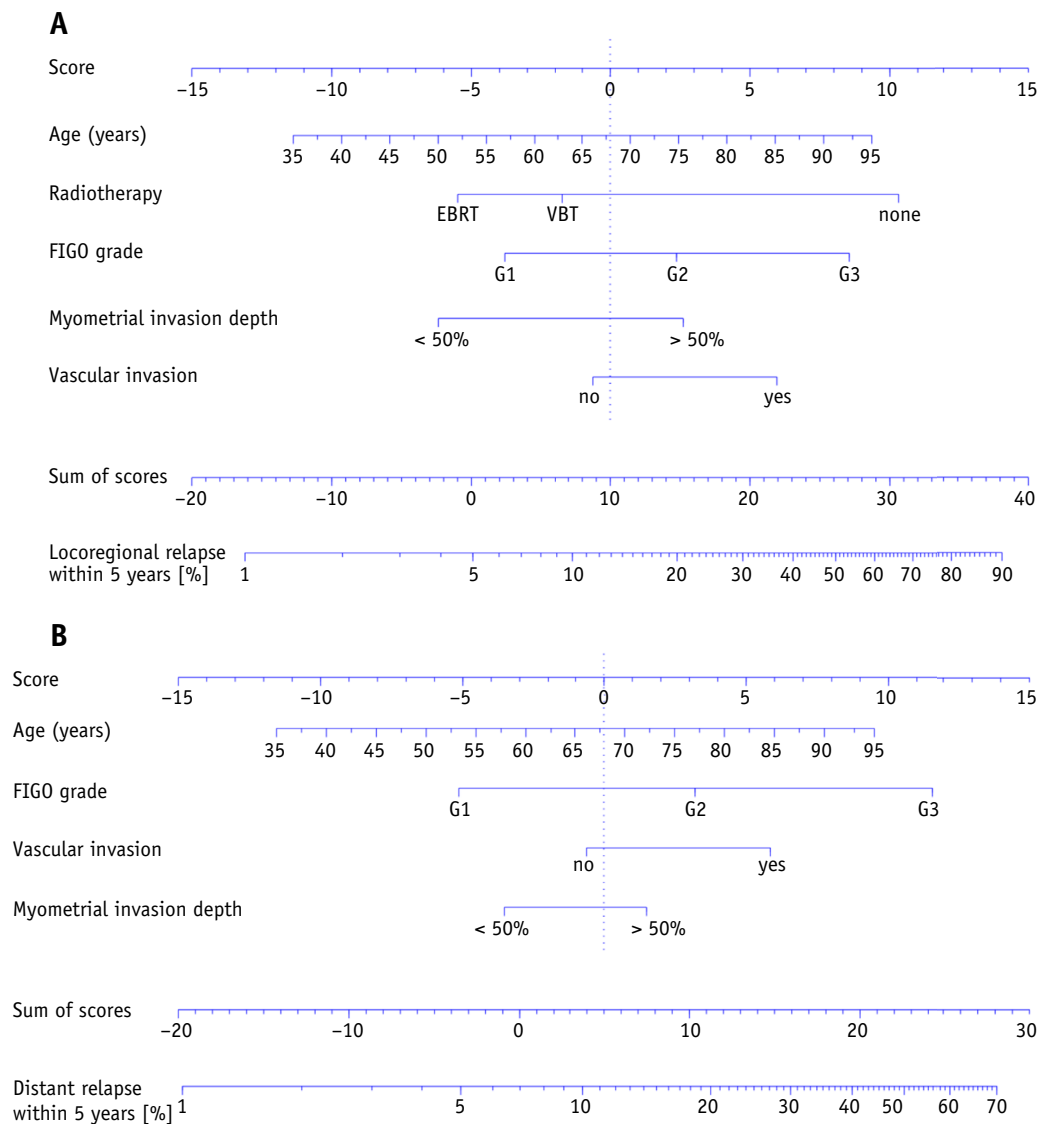


Fig. 1. Nomograms for (A) locoregional recurrence, (B) distant relapse, (C) disease-free survival, and (D) overall survival based on the final trial cohort (with revised pathology data). EBRT and VBT should not be added (as the series did not include patients who had both) but used separately. EBRT = external beam radiation therapy; FIGO = International Federation of Gynecology and Obstetrics; G = grade; VBT = vaginal brachytherapy.

of the pros and cons of such treatment decisions and should be able to make their own informed choices (9). In a specific treatment preference study, EC patients reported a relatively low minimally desired benefit of VBT (0%-8%) at which they would prefer VBT over a watchful waiting approach (10). The current nomogram would be an easy and understandable instrument to be used in shared decision making, to facilitate understanding of the individual risk profile, and to discuss whether pelvic EBRT or VBT would be useful for the specific situation. In other cancer types, where the decision to use adjuvant treatment is based on risk factors, such as in breast cancer, prediction models such as the Web-based program Adjuvant! Online have been implemented in clinical practice worldwide (19). Using such support systems greatly facilitates patient understanding of risks and benefits of adjuvant therapy, and

having such models for EC would facilitate shared decision making and also tailor the use of health care resources to the higher risk groups. In addition, the nomograms can also be used for selection of patients for clinical trials of adjuvant treatments and for generation of new hypotheses.

A limitation of our study is the relatively limited number of patients in the validation groups and the fact that the validation groups had less performance in the validation of LRR. Both the fact that the 2 validation sets did not include patients with (high) intermediate risk factors who were treated with surgery alone, and the relatively low number of LRR events contributed to the lower c-index. However, the performance of the validation for DR, DFS, and OS was excellent. We aimed to avoid overfitting by reducing the amount of predictors in the nomogram, by using the backward feature selection method.

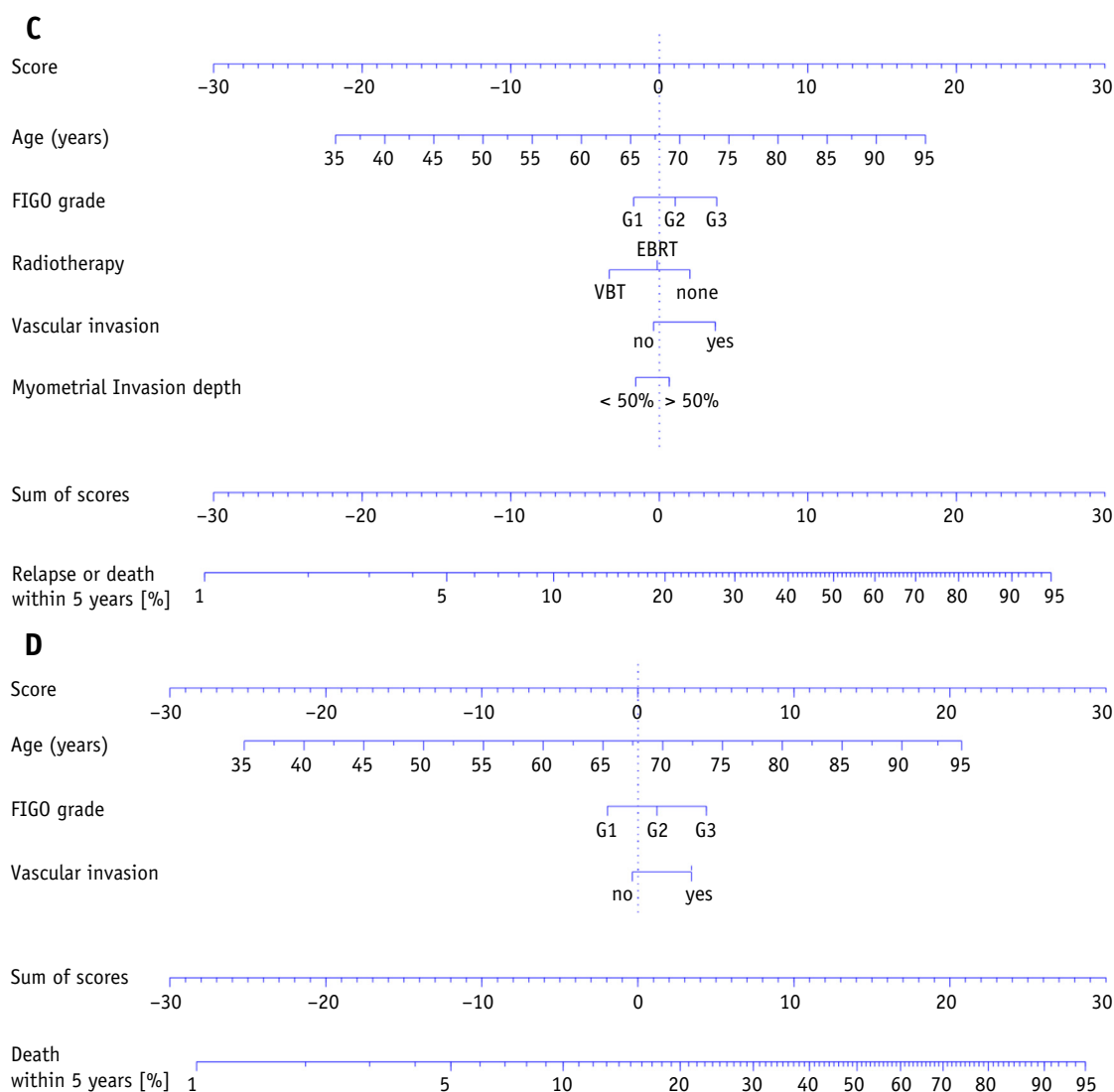


Fig. 1. Continued.

Another limitation is that the nomograms should be interpreted with caution for patients who have higher risk factors other than the large pooled group of patients with (high-) intermediate-risk stage I endometrial carcinoma on which the nomograms have been built, as has been illustrated in [supplementary Table E5](#) (available online at www.redjournal.com). For patients who have all high-risk factors (advanced age, grade 3, LVSI, deep invasion), the model seems to somewhat overestimate recurrence rates.

The fact that many EC patients have comorbidities and approximately 50% of deaths are due to causes other than EC is well known. Still, it is relevant when discussing adjuvant treatment with a patient to know how the likelihood of survival with and without relapse will be; in future, such information could be added using the patient's comorbidity profile as also used in other prediction models such as Adjuvant! (19). Combined analysis and validation with the Australian nomogram (13) is being planned.

A limitation of all current nomograms are that they take into account only classic clinicopathological risk factors. They only give a rough estimate of the patient's expected outcome. In our analysis, the classic risk factors increasing age, higher FIGO grade, and presence of LVSI were consistently selected for all outcomes, LRR, DR, DFS, and OS. For LRR, which is the main outcome that is influenced by pelvic EBRT and VBT in early stage EC, we found FIGO grade to have the highest HR, and grade was of stronger significance than LVSI and depth of myometrial invasion. Invasion of the cornuae, where the myometrium is thinnest and myometrial invasion is usually relatively close to the serosa but which may not be consistently reported in pathology reports, had the lowest impact and could be omitted. Both this and recent analyses suggest that LVSI may be the strongest factor for DR and survival (especially if extensive LVSI is taken into account), and the prognostic information of LVSI might be at least as strong as that of microscopic nodal involvement (20-22).

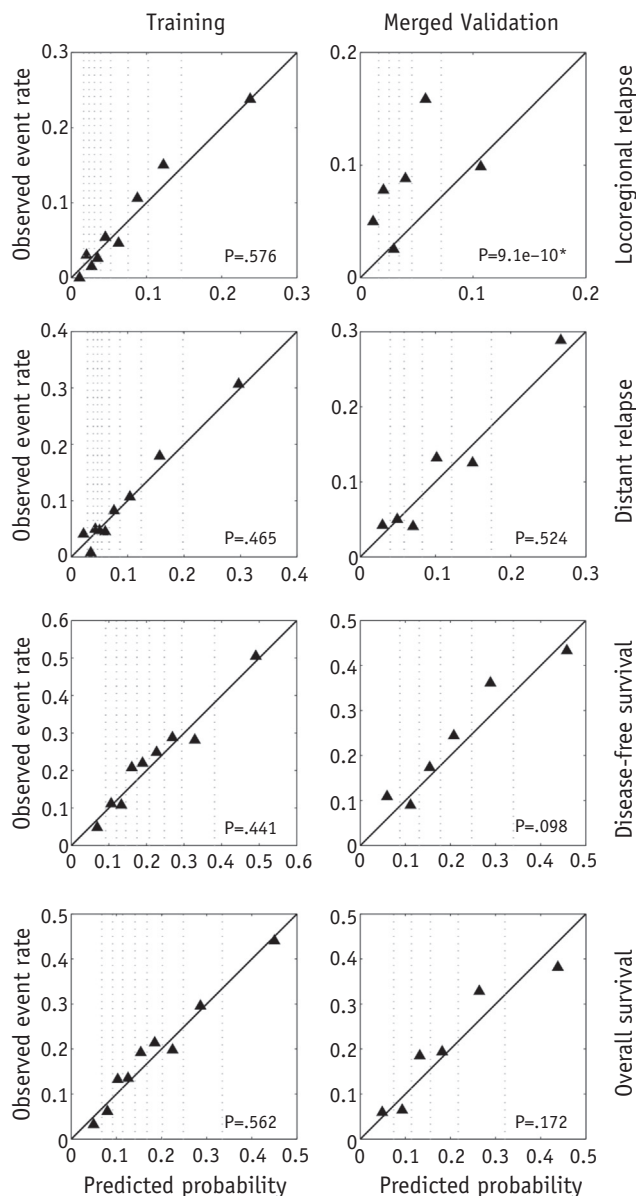


Fig. 2. Calibration plots show predicted event rates versus observed event rates for equally sized subgroups of patients. There are 9 subgroups for the training datasets and 6 for the merged validation dataset. Hosmer-Lemeshow statistic was used to compute *P* values for significant under- or overestimation of observed probabilities by the nomograms.

Conclusions

Although these nomograms are very useful in current risk prediction and for shared decision making about adjuvant treatment, addition of molecular genetic risk factors such as L1 cell adhesion molecule (L1CAM) expression, *POLE* proofreading mutations, *TP53* mutation, microsatellite-instability (MSI) and combinations thereof (7, 8) or of the rhw molecular signature (23) in risk prediction models might lead to much greater precision of the risk estimates, and in

future nomograms, such features should be incorporated. These nomograms for use in patient counseling and shared decision making are able to accurately predict long-term outcome in terms of locoregional recurrence, distant recurrence, and survival with or without adjuvant EBRT or VBT.

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